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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/109,858	07/02/98	RAO	M T5530.CIP

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EXAMINER	
KERR, J	
ART UNIT	PAPER NUMBER
1633	10

DATE MAILED: 05/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/109,858	Rao et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *Mar 6, 2000* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *12, 15, 16, 21, 23, 24, 26-33, 35, 37, 43-45, and 49-59* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *12, 15, 16, 21, 23, 24, 26-33, 35, 37, 43-45, and 49-59* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Applicants' amendment, filed on 3/6/00, has been entered.

Claims 1-11, 13, 14, 17-20, 22, 25, 34, 36, 38-42, and 46-48 have been canceled.

Claims 12, 15, 16, 21, 23, 24, 26-33, 35, 37, 43-45, and 49-59 remain pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 37, 43, and 45-59 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record and the reasons below.

Claims 35, 37, 43, and 45-58 are directed to a method for treating a neurological or neurodegenerative disease comprising administering and effective amount of neuronal restricted precursors cells or derivatives thereof or mixtures thereof, and pharmaceutical compositions comprising neuronal restricted precursor cells.

Applicant's arguments filed 3/6/00 have been fully considered but they are not persuasive. Applicants argue that in view of the recitation of specific neurodegenerative diseases to be treated in the method, and recitation of the transplantation site of the neuron-restricted precursor cells to be used in the method of treating neurodegenerative diseases, and in view of the teachings in the specification regarding ranges for concentrations of cells to be administered, and appropriate sites of transplantation, the specification provides sufficient guidance to make and/or use the invention as set forth in the amended claims.

Applicants' arguments are not persuasive as the specification does not disclose any specific neuronal disorder which has been subjected to the claim-designated treatment regimen,

nor does the specification teach any specific methodology associated with such a treatment regimen including the number of cells to be administered for a specific neuronal disorder, the route of administration for a specific neuronal disorder, or the relevant cell therapy target site for the specific neuronal disorder such that treatment of the disorder is effected. The specification does not provide any correlation between a specific neuronal disorder and a specific means by which such a disorder can be treated. Moreover, the specification does not provide any working examples which establish that the claim-designated neuronal disorders, such as Parkinson's disease, Huntington's disease, Alzheimer's disease, dysfunctions resulting from injury or trauma, amyotrophic lateral sclerosis, or anencephaly are amenable to treatment with administration of neuron-restricted precursor cells which may contain a gene encoding a therapeutic protein of interest. In addition, as stated in the office action of 10/14/99, the state of the art at the time of filing teaches that neuronal transplantation techniques and *in vivo* therapeutic effectiveness have not been established such that utilizing cells to treat neuronal disorders is routine or predictable.

In view of the lack of working examples in the specification, the teachings in the art at the time of filing that cell and gene therapy strategies for treating neuronal disorders are not well established and are still problematic, and in view of the lack of guidance in the specification as to specific protocols in which the clinical efficacy of the claim-designated methods has been established, one of skill in the art would not be able to use the claim-designated methods or claim-designated cells predictably and without undue experimentation.

Claim 59 is drawn to a method of isolating a pure population of mammalian CNS neuron-restricted precursor cells which requires a sample of mammalian embryonic stem cells.

Applicants argue that the claimed invention, as amended, is enabled by the teachings in the specification. Applicants assert that in view of the teachings of Thompson *et al.*, which demonstrate neuronal differentiation in human ES cells, one of skill in the art would know how to obtain ES cells for use in the instant invention (see page 12 of applicants' Response). The specification is not enabling for isolating a pure population of human CNS neuron-restricted

precursor cells using human embryonic stem cells as a starting material. As discussed in the office action of 10/14/99, for a population of cells to be defined as embryonic stem cells, establishment that the embryonic stem cells retain their totipotential capacity and are able to generate cells of all lineages, including germline, after being introduced into host a blastocyst, is necessary. This has not been demonstrated either in the specification or in the reference of Thompson *et al.* Absent a showing of totipotency, and in view of the teachings in the art at the time of filing that establishing embryonic stem cells in species other than mice is neither routine nor predictable, the claimed invention is not commensurate in scope with the teachings of the specification. In view of the lack of guidance in the specification with regard to the process of obtaining human embryonic stem cells, the use of the cells in the claimed cell culture method is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 15, 16, and 26 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is rendered vague and indefinite for the following reasons: the phrase "NEP medium configured for inducing said cells to begin differentiating" is confusing because it is unclear if the cells are incubated in NEP medium, as defined in the specification, or if the NEP medium is altered such that it induces the cells to begin differentiating. If it is the former, the phrase "configured for inducing" should be changed to "to induce"; and the phrase ""wherein said neuron-restricted precursor cells require FGF" is vague as it is unclear if the cells require FGF in step (b) of the method to induce differentiation, or if FGF is required in step (d) for supporting adherent growth of the purified subpopulation of cells. Clarification is requested. Moreover, it is

unclear what culture conditions are required which support adherent cell growth and which result in the differentiation of the cells into CNS neuronal cells but not CNS glial cells.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 23, 26, and 27 remain rejected under 35 U.S.C. 102(b) as being anticipated by Blass-Kampmann *et al.* (J. Neuroscience Research 37:359-373, 1994) for the reasons of record and the reasons below.

The claims are drawn to a composition containing a pure population of neuron-restricted precursor cells.

Applicant's arguments filed 3/6/00 have been fully considered but they are not persuasive.

Applicants rely on the Declaration by Dr. Mahendra Rao, submitted 3/6/00, to argue that the cells of the instant invention and the prior art cells are distinct. Applicants argue that the characteristics of the cell populations of the instant invention differ from those of Blass-Kampmann *et al.* in their ability to differentiate into glial cells, their growth factor requirements, and their survival times, i.e., the cells of the instant invention do not differentiate into glial cells, FGF is required, serum feeding results in cell death, and the cells of the instant invention grow over multiple passages. This is not persuasive as the method steps recited in the claims which produce the cells of the instant invention are not distinguishable over the prior art method steps. There is no recitation in the claimed methods of specific culture conditions, i.e., the inclusion of FGF in a particular step, or the omittance of fetal calf serum, nor is there any recitation of the lifespan of the cells obtained in the culture method. Although the claims recite the limitations "wherein said neuron-restricted precursor cells require FGF and differentiate into CNS neuronal

cells but not into CNS glial cells", these limitations would be inherent to the cell population produced by the method of the instant invention as well as the prior art method. Thus, the method of producing the population of cells and the cells produced by the method are necessarily the same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12, 15, 16, 24, 28-33, and 44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Blass-Kampmann *et al.* (J. Neuroscience Research 37:359-373, 1994), taken with Boss *et al.* (U.S. Patent No. 5,411,883, 1995), Weiss *et al.* (WO93/01275, 1993), Johe *et al.* (U.S. Patent No. 5,753,506, 1998, effective filing date of 5/23/96), Rao *et al.* (26th Annual Meeting of the Society for Neuroscience, 22:527, Abstract #215.12, 1996), and Lee *et al.* (U.S. Patent No. 5, 175, 103, 1992) for the reasons of record and the reasons below.

Applicant's arguments filed 3/6/00 have been fully considered but they are not persuasive.

Applicants argue that the reference of Blass-Kampmann *et al.* teaches cells which do not require FGF and which differentiate into both neurons and glial cells. Applicants further argue that the secondary references do not remedy the deficiencies of the primary reference. Applicants rely on the Declaration of Dr. Rao which states that the cells taught by Boss differentiate into different neurons, i.e., dopaminergic neurons and have different growth factor requirements, i.e., do not require FGF, from the cells of the present invention. The argument with regard to the Blass-Kampmann *et al.* reference has been discussed in the above rejection. With regard to the cells of Boss, it is noted that the claimed invention in the instant application does not recite any limitation with respect to the type of differentiated neuron. Moreover, as previously stated, it is not clear at what point in the claimed incubation procedure the FGF is required such that the cells are restricted to differentiation into neuronal but not glial cells. In addition, Boss was relied upon to disclose that selections of specific neuronal cell types can be performed using FACS, and magnetic bead antibody sorting and that neuron progenitor cells can be induced to differentiate *in vitro* by adding a differentiation agent to the culture medium. Similarly, Johe *et al.* was relied upon to disclose dissociating cells from various regions of embryonic brain and culturing the cells in the presence of *either* EGF or bFGF to allow proliferation of the cells, and that removing the mitotic agent resulted in differentiation of the cells. In addition Weiss *et al.* disclose methods of differentiating neuronal precursor cells by including basic fibroblast growth factor. Furthermore, Rao *et al.* disclose that cultures of E10.5 neuroepithelial cells from the rat caudal neural tube require both FGF and chick embryo extract to proliferate and to maintain an undifferentiated phenotype, and Lee *et al.* disclose that NT2 cells can be differentiated into greater than 95% pure cultures of neuronal cells when cultured in the presence of retinoic acid, and that the neuronal cells can be maintained in a post-mitotic state after withdrawal of mitotic inhibitors.

Applicants assert that the references neither alone or in combination teach a neuron-restricted precursor cell which only differentiates into neuronal cells and not glial cells, and which requires FGF in the culture method. In addition, applicants assert that neurons can be obtained from cell populations via methods such as those taught by Weiss *et al.*, Johe *et al.*, Rao *et al.*, and

Lee *et al.*, although dividing neuronal precursors that differentiate solely into neurons had not bee shown to develop from any of the cell populations described in the art. This is not persuasive, however, in view of the similar starting materials and culture methods of the prior art and the instant application, the claimed methods would necessarily result in the claimed cell population. It is suggested that applicants amend the method claims to distinguish the initial and final cell populations of the method, to define the incubation protocols, and further to define the final cell product obtained as to its morphologic and phenotypic characteristics to overcome the prior art of record.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via

the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

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